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Quine Intellectual Property Law Group, P.C.

By:

Attorney Docket No: 407J-896410US
Client Ref: 97-247-2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Peter J.Kushner

Application No.: 09/103,355

Filed: June 23, 1998

For: METHODS FOR SCREENING NUCLEAR TRANSCRIPTION FACTORS FOR THE ABILITY TO MODULATE AN ESTROGEN RESPONSE

Examiner: Michael Pak

Art Unit: 1646

DECLARATION UNDER 37 C.F.R. § 1.132

DECLARATION OF PROFESSOR THOMAS S. SCANLAN

1. I, Thomas Scanlan, am Professor of Chemistry, Pharmaceutical Chemistry, and Cellular & Molecular Pharmacology, as well as a member of the Graduate Group in Biophysics and a member of the Molecular Design Institute at the University of California, San Francisco (UCSF). I am also a member of the Herbert Boyer Program in Biological Sciences (PIBS) and a program member of the UCSF Comprehensive Cancer Center. I have been a chemist and biochemist for more than 20 years in the area of small molecule-protein interactions and receptor-mediated signal transduction. In particular, a focus of my research has been on receptor-ligand interactions of members of the nuclear receptor superfamily. I am author of over 50 peer reviewed publications, and am co-inventor of 8 issued patents and 2 patent applications.

2. I am not a co-inventor of the subject matter claimed in United States Patent Application Number 09/103,355, nor do I have any financial or other interest in any rights connected thereto. I am currently, and have been since 1989, employed by the Regents of the University of California.

3. I have read the above-referenced patent application (including its specification and claims pending as of October 31, 2003), as well as the following correspondence between the Applicants and the Examiner:

1) Office Action Dated March 12, 2002

2) Response filed September 9, 2002

3) Office Action Dated February 10, 2003

4) Response filed (with this declaration).

4. I have been asked to comment on the following issues: 1) whether the scope of the term "nuclear transcription factor ligand" would be clear to a person having ordinary skill in the art;

2) whether the scope of the term "cognate receptor" would be clear to one of skill in the art; and, 3) whether the specification provides adequate instruction for one of skill in the art to practice the claimed method. I understand that my comments are to be based solely on the disclosure in the application and on the common knowledge in this field as of a date no later than June 30, 1997 (priority date, filing date is June 23, 1998).

5. Nuclear Transcription Factor Ligand

It is my understanding based on the Office Actions dated March 12, 2002 and February 10, 2003, that the Examiner believes that the "metes and bounds" of the term "nuclear transcription factor ligand" are unclear. By this, I understand the Examiner to be saying that one of ordinary skill in the art at the time the application was filed would not be able to determine whether a particular molecule was categorized as a "nuclear transcription factor ligand." I respectfully disagree. Based on the information in the specification and common knowledge in the art, the scope of the term "nuclear transcription factor ligand" is clear. The term "nuclear transcription factor ligand" is defined in the specification, on page 6, lines 1-2, as a compound that binds a "nuclear transcription factor." The specification, at page 5, line 30 defines "nuclear transcription factor" as referring to members of the nuclear transcription factor superfamily. Exemplary nuclear transcription factor ligands are given on p. 6, lines 3-5, and include estrogen, progestins, androgens, mineralcorticoids, retinoic acid, vitamin D, and prostaglandins. On page 6, lines 14-15, the specification states that the cognate receptor for an estrogen is an estrogen receptor, the cognate receptor for a glucocorticoid is a glucocorticoid receptor, for a progestin is a progestin receptor, and so forth. Prior to June 30, 1997, it was well known that the estrogen receptor, the glucocorticoid receptor, progestin receptor, androgen receptor, mineralcorticoid receptor, retinoic acid receptor, vitamin D receptor, prostaglandin receptor, as well as numerous additional receptors, e.g., thyroid receptor, all belong to a superfamily of structurally related proteins. That these nuclear transcription factors were recognized in the art as belonging to a structurally related superfamily of molecules is evidenced by numerous publications on the subject, including the following review articles and patents:

a) Evans **1988** "The Steroid and Thyroid Hormone Receptor Superfamily" Science 240:889-895.
b) Mangelsdorf et al. **1995** "The Nuclear Receptor Superfamily: The Second Decade" Cell 53:835-839.
c) Mangelsdorf & Evans **1995** "The RXR Heterodimers and Orphan Receptors" Cell 53: 841-850.
d) Ribeiro et al. **1995** "The Nuclear Hormone Receptor Gene Superfamily" Annual Review of Medicine 46:443-453.
e) USPN 5,639,592 to Evans **1997** column 1, lines 23-25.
f) USPN 6,004,748 to Pfahl & Karin **1999** (priority to 1990) column 1, lines 16-20.

Thus, while the ligands which bind to members of the nuclear transcription factor superfamily are diverse in nature and structure, the receptor molecules to which they bind are all related members of a molecular superfamily. The ligand or ligands which bind to numerous members of the nuclear transcription factor superfamily are known, and can be readily ascertained by those of skill in the art. Additionally, for any particular member of the nuclear transcription factor family, one of skill in the art is well versed in the performance of receptor binding assays to determine whether any particular molecule is a ligand for that receptor. Thus, it would have been perfectly clear to one of ordinary skill in the art as of June 30, 1997, what was meant by the term "nuclear transcription factor ligand" and whether any particular molecule met that definition with respect to any nuclear transcription

factor selected from the superfamily.

6. Cognate receptor

It is my understanding that the Examiner believes that one of ordinary skill in the art would not know what is meant by the term "cognate receptor" to be unclear. I disagree. The term "cognate" to refer to the members of a ligand-receptor pair has been in common usage in the art since well before the June 30, 1997. The specification at p. 6, line 13 provides a definition of the term "cognate receptor" that is fully consistent with this usage in the art, i.e., a cognate receptor is "a receptor of the type that is typically bound by the transcription ligand in question. On page 6, lines 14-15, the specification supplies specific examples consistent with this meaning: "the cognate receptor for an estrogen is an estrogen receptor, the cognate receptor for a glucorcorticoid is a glucocorticoid receptor, for a progestin is a progestin receptor, and so forth." The amended claims specify that the cognate receptor belongs to the nuclear transcription factor superfamily, as discussed above. Thus, it would have been obvious to one of ordinary skill in the art at the time this application was filed, that the term cognate receptor referred to a member of the nuclear transcription factor superfamily that binds to a specified ligand, i.e., the ligand for which the practitioner is evaluating the ability to modulate estrogen mediated transcriptional activation via binding at an AP-1 site.

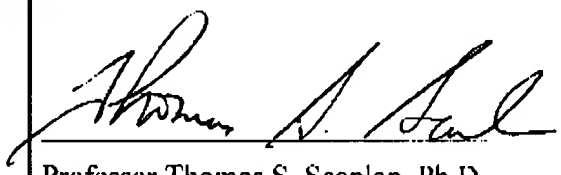
7. Instruction required to practice the claimed method.

It is my understanding that the Examiner is of the opinion that the subject application does not provide sufficient information to have enabled a person of ordinary skill in the art to practice the claimed methods due to the hypothetical existence of non-functional embodiments. Specifically, I understand the Examiner to be saying the a practitioner of ordinary skill would not be able to practice the invention because certain of the nuclear transcription factors are "orphan receptors" and/or because of the existence, either actual or theoretical, of non-functional variants of certain nuclear transcription factors of known binding characteristics. Neither the existence of receptors for which the binding characteristics are currently unknown, nor the existence of non-functional variants of nuclear transcription factors prevents a person skilled in the art from fully practicing the invention. Because the receptor is selected with respect to the ligand of interest, a practitioner desiring to "screen a nuclear transcription factor ligand for the ability to modulate estrogen activation at an AP-1 site" would recognize, based on the information in the specification, that the cognate receptor, that is, the receptor to which the ligand is normally bound, is the appropriate receptor with which to practice the method. "Orphan receptors" are receptors for which the ligand is not presently known. Because of this fact, one of skill in the art desiring to evaluate potential modulation of estrogen activation by a particular ligand would know not to perform the method with a receptor for which the ligand was not known as of the date the practitioner was performing the method. Similarly, with respect to a receptor of known binding properties, one of skill would recognize that in order to evaluate the ability of a ligand to modulate activity of the estrogen receptor, a functional receptor for the ligand is desirable. Numerous such functional receptors have been reported and are known, or can be readily ascertained, by those of skill in the art. Indeed, where variants have been described, they are typically characterized in relation to the known wild-type functional receptor. Thus, for any cognate nuclear transcription factor receptor, it is a trivial matter for the practitioner to select a version of the receptor that is functional. For example, by comparing the sequence of the receptor in question to the sequence of the wild type cognate receptor for a ligand of interest, a practitioner can easily tell if he or she has obtained a

cognate receptor for the ligand which is functional. The mere fact that certain variants would not be functional in no way prevents a person knowledgeable in the art from selecting an appropriate cognate receptor that is functional in the screening methods of the invention, and practicing the invention as claimed.

8. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon

Declarant's signature:



Professor Thomas S. Scanlan, Ph.D.

Nov. 12, 2003
Date